A Split-face Double-blind Randomized Placebo-controlled Trial of the Effectiveness of 5% *Kaempferia parviflora* Extract for Treatment of Melasma

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ABSTRACT

Background: Melasma is a common hyperpigmentary disorder that can cause significant psychosocial distress and quality of life impairments. Krachaidam (*Kaempferia parviflora)* extract is well known for its several methoxy flavones that has the anti-tyrosine activity and can inhibit the effect in melanin synthesis which can relief of melasma.

Objective: To research the effectiveness and satisfaction of 5% *Kaempferia parviflora* extract topical cream for the treatment of melasma.

Method: 16 volunteers, female of age between 30 and 65 years old who willingly wanted to get rid of their melasma were collected to participate in split-face double-blinded placebo-controlled trial for 8 weeks. 5% *Kaempferia parviflora* extract cream and placebo cream were instructed to apply twice daily in designated sides of the face for 8 weeks. Various parameters such as melasma evaluation by dermatologists, MASI score and melanin index were assessed at the start, 4^{th} and 8^{th} week respectively.

Result: Statistically significant results of reduction in MASI score (p-value <0.001) and reduction in mean melanin index (p-value<0.001) were shown for *Kaempferia parviflora* extract treated side. No side effects were observed throughout the study.

Conclusion: This study statistically demonstrated that *Kaempferia parviflora* extract reduced melanin production more than placebo cream when it is applied topically with no harmful side effects. So, 5% *Kaempferia parviflora* could be safe, effective and can be used as an alternative for the treatment of melasma.

Keywords: *Kaempferia parviflora,* Krachaidam, Melasma, MASI score, Melanin index

1. Introduction

Melasma which is also known as acquired melanosis, characterized by symmetrical, irregular, light-to-dark brown macule on sun- exposed areas of skin such as malar prominence and upper cheek. The term melasma derives from the Greek word “melas” that means black due to its brownish clinical presentation. In the medical literature, the term cholasma originated from the Latin chloos and the Greek cloazein: greenish) is still used (Handel et al., 2014).

Quality of life is a broader concept, it defines one general well-being not only by wealth but also by other parameters such as physical and mental fitness, leisure time and so on. Facial appearance plays an important role in self-perception and interaction with others. Therefore, the patient who suffers melasma can cause a break in their social networks (Jiang et al., 2018). Hence, the treatment should target on both physical looking and mental fulfillment (Anderson, L., & Rodrigues, M., 2019).

The pathophysiology of melasma is undermined (Demirkan, S., Gunduz, O., and Sayan, C. D., 2017). The contributing factors are exposure to intense ultraviolet radiation, genetic predisposition and hormonal influences. Moreover, the treatment guidelines are still challenging due to non-persistent treatment result and frequent relapses. To achieve the most suitable treatment and procedure for melasma, different modalities in treatments inhibit the production of melanin or dispersion at different stages through different mechanisms (Bagherani, 2015).

Due to its recurrence nature, melasma is quite challenging to treat. The goals of treatment are prevention of recurrence, reduction of affected area, reduced time to clearance with fewest adverse effects and improvement in the cosmetic defect. Current treatments of melasma include application of sunscreen, use of topical HQ alone or in combination with tretinoin, and or a corticosteroid (Gupta et al., 2006). The choice of treatment options of their combination depends mainly on the type of melasma, effectiveness of prior treatments, and expectations of the patient.

Kaempferia parviflora (KP) or Krachaidam, which belongs to the family Zingiberaceae, is originally found in the North and Northeast of Thailand. It is also known as black ginger and popular as health-promoting herbs and used traditionally as a folk medicine for managing ulcers, gout, colic disorder, abscesses, allergy and osteoarthritis (Saokaew S., Wilairat P., and Raktanyankan P, 2017).

A number of pharmacological studies shown that it has antiallergenic, anti-inflammatory, antimutagenic, anti-depressive, anticholinesterase, antimicrobial, anticancer, anti-peptic ulcer, cardio- protective, anti-obesity activity and aphrodisiac. KP products are widely available in market as aphrodisiac booster (Sudwan et al., 2017).

In a study, compounds 5-Hydroxy-7,3,4 trimethoxyflavone, 5,7,3,4 Tetramethoxyflavone, 5,3-dihydroxy-3,7,4-trimethoxyflavone, and 5-hydroxy-3,7,3,4 tetramethoxyflavone inhibited the expression of tyrosinase, tyrosine-related protein (TRP)-1, and TRP-2 mRNA, which could be the mechanism of their melanogenesis inhibitory activity. It also identified several methoxy-flavones possessing potent melanogenesis inhibitory activity from a methanol extract of *Kaempferia parviflora* rhizomes. Some compounds were more potent than arbutin. In

particular, 5,3-dihydroxy-3,7,4 -trimethoxyflavone and 5-hydroxy-3,7,3,4 –tetramethoxyflavone were 60-fold more potent than arbutin (Ninomiya et al., 2016).

Kaempferia parviflora extract has potent anti-tyrosinase, anti-inflammatory and antioxidant activities, UV protection activities and skin moisturizing effects. Therefore, we plan to study the anti-tyrosinase activity which will be useful in inhibition of melanin production. But the extract still does not have reports on melasma study. Hence, the main purpose is to study the efficacy and satisfactory evaluation of topical Kaempferia parviflora extract cream for the treatment of melasma.

2. Objectives of the study

General Objective

To research the effectiveness and satisfaction of 5% *Kaempferia parviflora* extract topical cream for the treatment of melasma.

Specific Objective

- **Primary outcome**

To explore the whitening effect of facial skin for the treatment of melasma 5% *Kaempferia parviflora* extract cream.

- **Secondary outcome**

To observe the side effects of 5% *Kaempferia parviflora* cream in treating melasma

To assess the participants' satisfaction between 5% *Kaempferia parviflora* extract cream and placebo cream.

3. Materials and methods

Sixteen female volunteers with melasma who are between 30 to 65 years depending on the inclusion and exclusion criteria were enrolled in a double blinded, randomized split face controlled clinical trial. The *Kaempferia parviflora* cream was made of water, 5% *Kaempferia parviflora* rhizome extract, caprylic triglyceride, glycerin, dimethicone, C12-15 alkyl benzoate, behenyl alcohol, cetearyl alcohol, Jojoba seed oil, glyceryl stearate, propanediol, sodium polyacrylate, ethylhexyleglycerin, PEG-40 stearate, ceterareth-20, tocopheryl acetate, disodium EDTA. The researcher explained why and how the study would be performed and then took the history and physical examination of the volunteers for basic information. Informed consent from each volunteer was taken and Use test was performed. For randomization process, *Kaempferia parviflora* extract cream and placebo cream base (similar consistency, color and smell), were enclosed in the identical package. Then, they were labeled as "A" and "B" respectively. The participants and dermatologists, who have to evaluate the results, were all blinded. The physician, unrelated with the research, generated randomization sequence which was randomly determined which side of the participant' face to be treated with cream A and which side with cream B by using "Block

randomization" and concealed the sequences in opaque envelope. After randomization was done by the physicians, volunteers were instructed to apply 5% *Kaempferia parviflora* extract cream and placebo cream twice daily for 8 weeks consecutively. Volunteers had to apply sunscreen 30 minutes before sunlight exposure during the whole period of the study. Melasma Area and Severity Index (MASI) score and Mean Melanin Index by using Mexameter® together with VISIA® complexion analysis system was used to assess at the time of their attendance,4th week and 8th week respectively.

Sample Size Calculation

The calculation was done by using 2 means and standard deviation of the measurement from previous research which is the comparative study of the safety and efficacy of 75% mulberry (*Morus alba*) extract oil versus placebo as a topical treatment for melasma and a randomized, single-blind, placebo-controlled trial (Alvin et al., 2011).

Biophysical Technique

The photos of the volunteers were taken by VISIA® Complexion Analysis System, an equipment which scans the skin and captures the critical visual information by multispectral imaging and analysis of the areas what affects the appearance of skin, UV spot and brown spots. The mean melanin index, the parameter of the mexameter was measured by Mexameter® MX18. The severity of the melasma was determined by MASI score (Melasma Area and Severity Index).

Statistical Analysis

The data were obtained from patients' files and were analyzed statistically by using SPSS 18 software and Microsoft Excel 2010 in Dermatologic Clinic, Mae Fah Luang University Hospital.

4. Results

According to the demonstrated general characteristic of the participants, mean age of subjects was 46±7.86 years. Among them, fourteen subjects got exposed to sunlight with mean duration of 23.12+16.82 minutes. Among 16 subjects in this study, fourteen subjects had Fitzpatrick skin type IV and the rests had Fitzpatrick skin type V.

Melasma area and severity index (MASI)

Table 4.1 Statistical analysis of MASI score compare between 5% *Kaempferia parviflora* extract cream and placebo cream on 0, 4th and 8th week.

Mean MASI Score	5%*Kaempferia parviflora* cream	Placebo cream	p-value (a)
	Mean ± SD	Mean ± SD	
Week 0	12.69±2.79	12.40±2.62	0.432
Week 4	11.80±2.87	12.01±2.37	0.589
Week 8	11.21±2.68	12.25±2.49	0.008
p-value (b)	<0.001	0.125	

Data were analyzed between group with Paired t-test (a), within group with Repeated measure ANOVA (b), *Statistically significant at the 0.05 level.

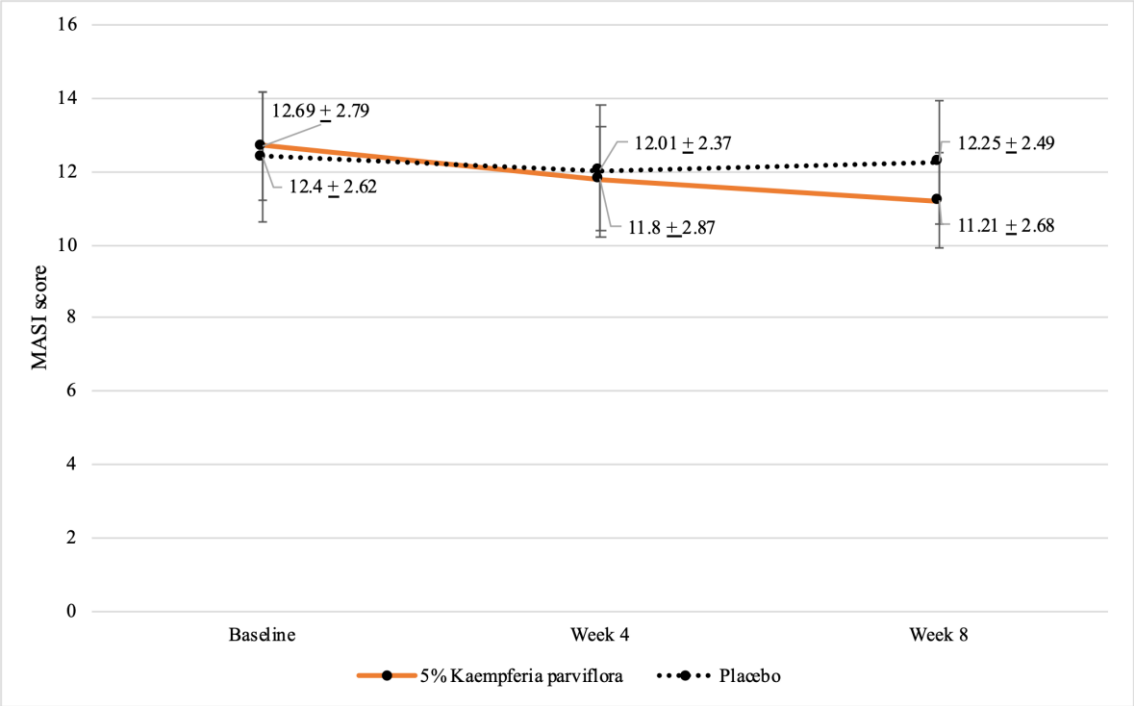

Figure 4.1 Linear graph show comparison of MASI score in each visit between 5% *Kaempferia parviflora* extract cream and placebo cream.

According to the statistical analysis results from table 4.1 and Figure 4.1, mean of MASI score in 5% *Kaempferia parviflora* extract cream and placebo cream before the treatment was 12.69±2.79 and 12.40±2.62 respectively at baseline. The mean of MASI score in 5% *Kaempferia parviflora* extract cream, the results after

treatment were at 4th week 11.80±2.87 and 8th week 11.21±2.68. The mean of MASI score in 5% *Kaempferia parviflora* extract cream decreased statistically significant at the level of 0.05 ($p<0.001$). For placebo cream, the results were at 4th week 12.01±2.37 and 8th week 12.25±2.49. The mean of MASI score in placebo cream was not statistically significant at the level of 0.05 ($p=0.125$). The comparison of MASI score between 5% *Kaempferia parviflora* extract cream and placebo cream; It found that mean of MASI score of 5% *Kaempferia parviflora* extract cream was significantly lower than MASI score of placebo cream at 8th week ($p=0.008$).

Mean Melanin Index Value Measured by Mexameter® MX18

Table 4.2 Statistical analysis of Mexameter compare between 5% *Kaempferia parviflora* extract cream and placebo cream on 0, 4th and 8th week using paired t-test and repeated measure ANOVA test

Mean Melanin Index	**5%Kaempferia parviflora**	**Placebo Cream**	**p-value (a)**
	Mean ± SD	**Mean ± SD**	
Week 0	260.27±45.09	260.02±44.98	0.961
Week 4	253.33±46.02	254.44±42.68	0.802
Week 8	247.58±44.59	258.08±43.35	0.017
p-value (b)	<0.001	0.061	

Data were analyzed between group with Paired t-test (a), within group with Repeated measure ANOVA (b)

*Statistically significant at the 0.05 level.

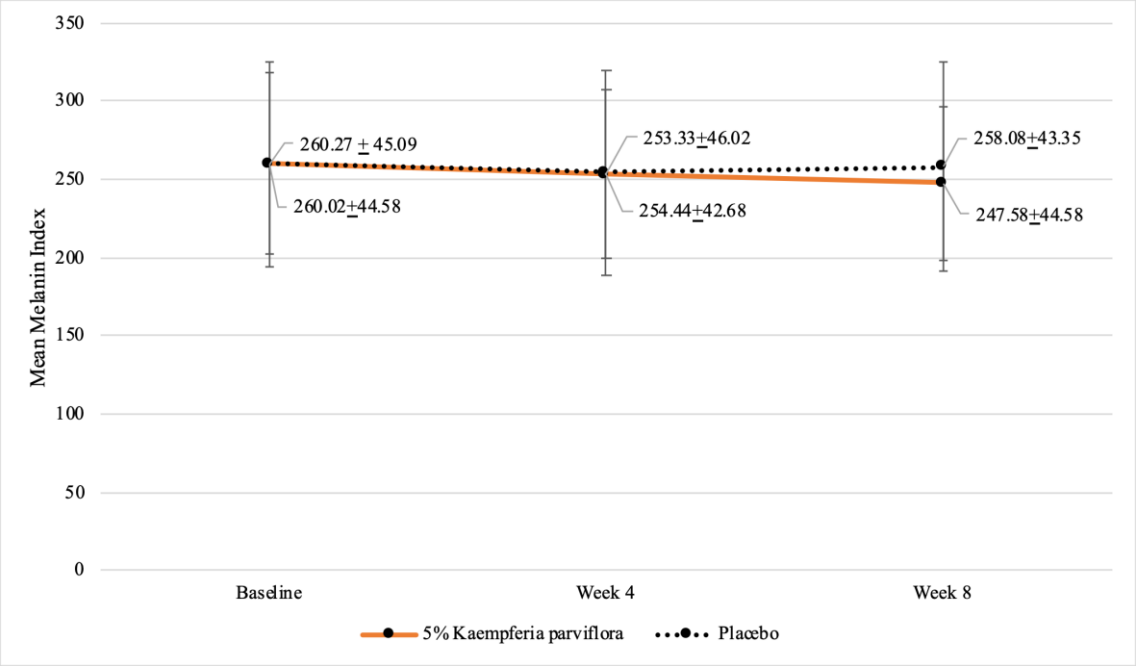

Figure 4.2 Linear graph show comparison of mean melanin index score in each visit between 5% *Kaempferia parviflora* extract cream and placebo cream.

According to the statistical analysis results from table 4.2 and Figure 4.2, the mean melanin index before the treatment with *Kaempferia parviflora* extract cream (from 260.27±45.09 to 247.58±44.59) and placebo cream (from 260.02±44.98 to 258.08±43.35) showed statistically significant reduction (p-value = 0.017) from the baseline to 8th week correspondingly with paired t-test. But, by using repeated measure ANOVA test, only *Kaempferia parviflora* cream side showed statistically significant result (p-value = <0.001) whereas the results from placebo cream side showed no significant improvement (p-value = 0.061). The researcher did the following at significance level of p-value <0.05.

Dermatologist Evaluation

Table 4.3 Statistically analysis of dermatologist evaluation score compared between *Kaempferia parviflora* cream and placebo cream on 4th and 8th week.

Improvement	Week 4		Week 8	
	Kaempferia parviflora	**Placebo**	***Kaempferia parviflora***	**Placebo**
100%=Excellent	-	-	-	-
75% = Good	-	-	1	-
50%=Moderate	3	1	6	2

Improvement	Week 4		Week 8	
	Kaempferia parviflora	Placebo	*Kaempferia parviflora*	Placebo
25% = Fair	10	8	9	11
0 = No change	3	7	-	3
-1= Worse	-	-	-	-

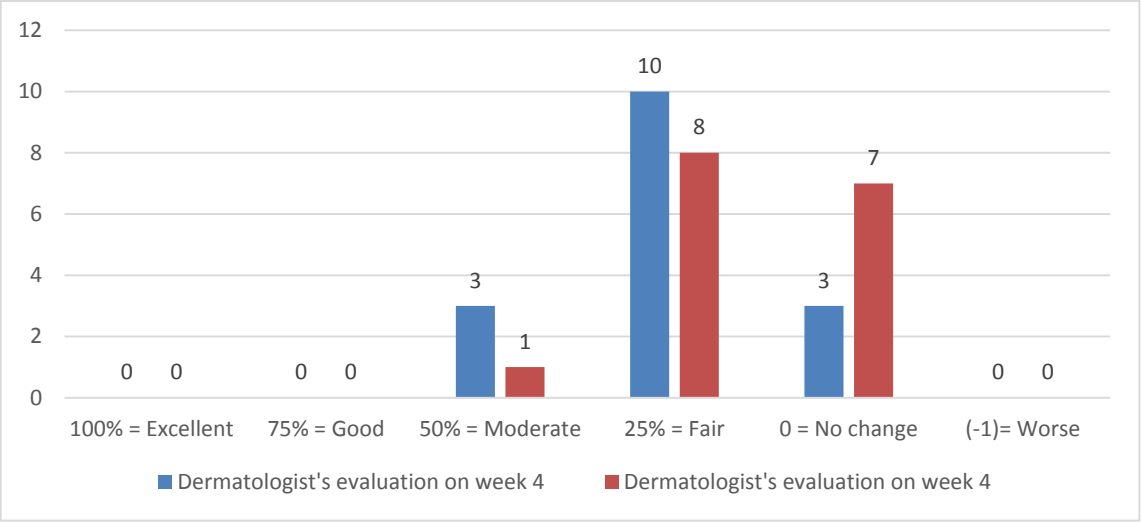

Figure 4.3 Column chart reveals the dermatologists' evaluation scoring of *Kaempferia parviflora* extract cream and placebo cream on 4th week

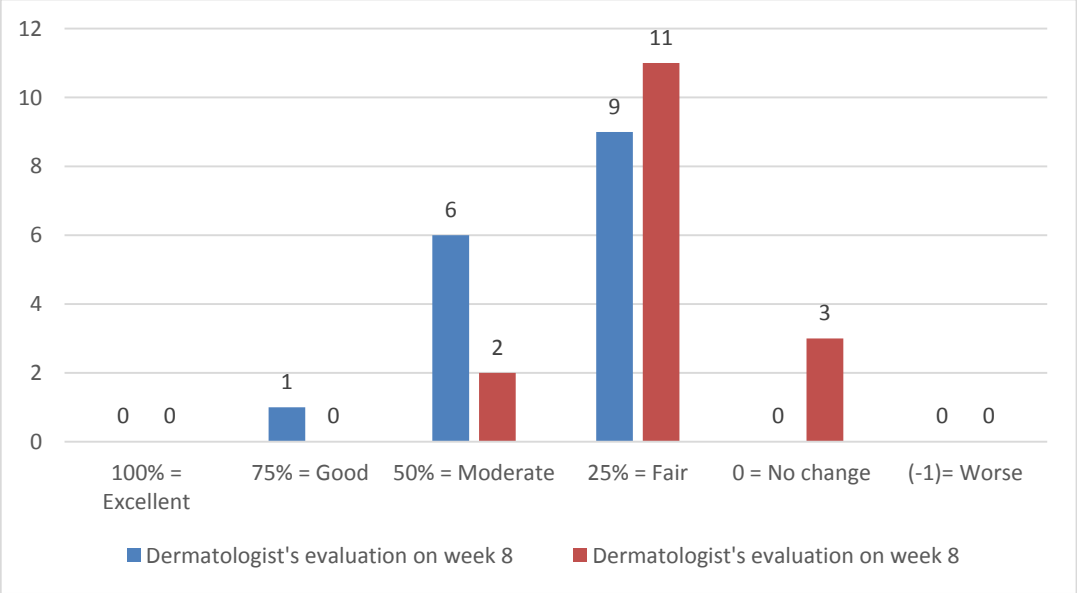

Figure 4.4 Column chart reveals the dermatologists' evaluation scoring of *Kaempferia parviflora* extract cream and placebo cream on 8th week

As described in Table 4.3 and Figure 4.3 and 4.4, 5% of *Kaempferia parviflora* extract cream and placebo cream applied on 4th week were evaluated by dermatologists and more than half of the volunteers improved fairly on *Kaempferia parviflora* cream side while nearly half of those showed fair improvement on placebo cream side. Three volunteers showed moderate improvement and another three volunteers showed no changes on the *Kaempferia parviflora* cream side. As for placebo cream side, only one volunteers improved moderately but half of those didn't change anything at all.

On 8th week of evaluation, the difference between two creams was seen clearly. For *Kaempferia parviflora* cream side, one volunteer started to show good improvement and for the resting fifteen volunteers, six of them showed moderate improvement and nine of them showed fair improvement. Meanwhile on the placebo cream side, three volunteers were still the same with no changes, eleven of those showed fair improvement and only 2 volunteers were seen moderate improvement.

Patient's satisfaction

Table 4.4 Statistical analysis of patient satisfaction score on 8th week on sides *Kaempferia parviflora* cream and placebo cream was applied

	5%*Kaempferia parviflora*	**Placebo**	**p-value**
	n (%)	**n (%)**	
Less than or equal to moderately satisfied (≤2)	6 (37.5)	14 (87.5)	0.008
Very/extremely satisfied (>2)	10 (62.5)	2 (12.5)	

P-value determined by the McNemar's Test

*Statistically significant at the 0.05 level

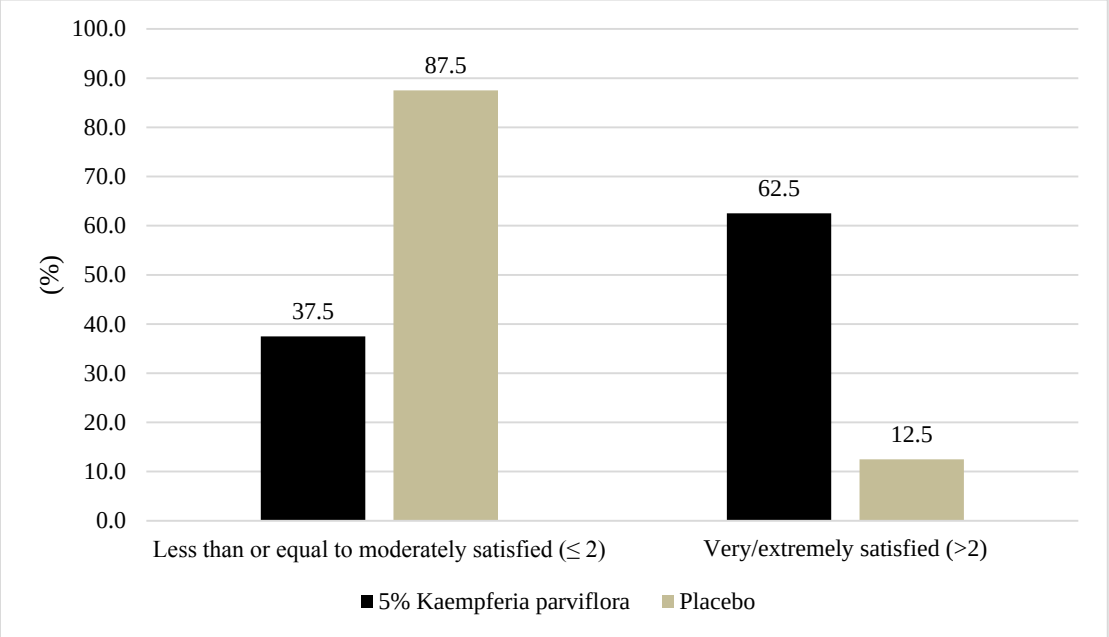

Figure 4.5 Bar chart reveals the percentage of patients' satisfaction score of 5% *Kaempferia parviflora* cream and Placebo cream

According to the statistical analysis results from table 4.5 and figure 4.5 showed patients' satisfaction score on 8th week, the results showed that in 5% *Kaempferia parviflora* extract cream were very/extremely satisfied (>2 score) 62.5% and Less than or equal to moderately satisfied (≤ 2 score) 37.5%.

For placebo cream, most of the subject rated less than or equal to moderately satisfied (≤ 2 score)87.5% and very/extremely satisfied (>2 score) 12.5% respectively. The comparison of patients' satisfaction score between 5% *Kaempferia parviflora* rhizome extract cream and placebo cream showed that statistically significant difference ($p=0.008$). The researcher did the following at significance level of p-value <0.05).

5. Discussion

Melasma, the most common facial hyperpigmentation, has psychological impact causing important quality of life issues due to cosmetic configurement (Tzouveka, 2014). The aim of the treatment is to slow down the proliferation of melanocytes, to inhibit the formation of melanosomes and to promote their degradation. Topical tyrosinase inhibitors can block melanogenesis leading to depigmentation.

Plant active compounds become popular during these days. Whitening agents containing natural ingredients can be used for long-term with minimal side effects (Brandyopadhyay, 2009). In this study, the *Kaempferia parviflora* extract cream was used to evaluate the anti-tyrosinase activity. *Kaempferia parviflora* extract has potent anti-tyrosinase, anti-inflammatory and antioxidant activities, UV protection activities and skin moisturizing effects (Amic et al., 2007). They also have anti-aging activity, anti-photoaging activity, anti-acne activity and anti-allergic activity.

This study is a double-blinded, randomized, placebo-controlled and split-face clinical trial. Sixteenth volunteers with melasma were recruited. MASI score and mean melanin index of the melasma were studied for 8 weeks with baseline, 4th, 8thweek follow-up and dermatologists and patients' satisfactory score were taken at 8th week of study.

Both MASI score and mean melanin index showed significantly better result in 5% *Kaempferia parviflora* treated side. When comparing of two sides, *Kaempferia parviflora* treated side statistically increased in 8th week follow-up phase but placebo side did not show any significant change at all. Three dermatologists evaluated as good (75%) improvement for 2 volunteers and more than half as moderate (50%) improvement on *Kaempferia parviflora* extract cream side whereas most of the placebo cream side was evaluated as fair (25%) improvement. For patients' satisfaction score assessment, *Kaempferia parviflora* extract cream also has gotten higher score than placebo cream after the 12 weeks study. Volunteers were very satisfied with the *Kaempferia parviflora* extract cream and were involved actively throughout the study. No significant or serious side effects were noted throughout the study period.

The melasma is a chronic condition even though there is no exact etiology and can be worsened by many factors like prolong sun exposure, hormonal treatments. Topical treatment with natural plant extract was not indicated to completely stop melanin production. Even though the results are satisfactory, limitations like small sample size and limited study period can cause difficulties in interpretation of the results. To sum up, *Kaempferia parviflora* extract cream has anti-tyrosinase activity to a certain extent. This can be one useful alternative treatment when topical agent such as hydroquinone is not tolerable. *Kaempferia parviflora* extract cream can reduce melanin production in human with low cost and offer other benefits as a strong antioxidant with less and minimal side effects.

6. Conclusion

According to this study result, 5% *Kaempferia parviflora* extract cream was able to reduce melanin production in volunteers. It had significant better outcomes in all aspects compared with placebo cream. There was no objection and side effects during the study period. Although the lowest concentration (5%) was used in this research, the volunteers were satisfied with the results. Therefore, 5% *Kaempferia parviflora* extract cream is effective and safe to use in treating melasma.

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